UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

3/6/00

MEMORANDUM

SUBJECT: **Vinclozolin.** Rationale for the Selection of the Field Trial Database for the Generation of Anticipated Residue Estimates for Use in the Preliminary Human Health Risk Assessment (Chemical I.D. No. 113201, DP Barcode D261894)

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INTRODUCTION

At an 11/23/99 meeting held between the Agency and BASF Corp., BASF was informed that the Health Effects Division (HED) was planning to use field trial data as opposed to monitoring data to derive anticipated residue (AR) estimates to refine dietary exposure in the preliminary **Vinclozolin** human health risk assessment. HED's basis for this was that field trials measured all regulated residues whereas monitoring data typically included residues of the parent compound only. However, HED informed BASF that they may attempt to demonstrate that a reliable ratio exists between the parent compound and all residues of toxicological concern. In response to this discussion, BASF has submitted rationale for the use of select plant metabolism studies to derive a ratio between vinclozolin per se and all regulated/toxicologically significant residues, i.e., those containing the 3,5-dichloroaniline (3,5-DCA) moiety. This ratio, its basis, and HED's response are presented below.

BASF FACTOR AND SUPPORTING RATIONALE

BASF summarized the results of four of the available seven plant metabolism studies; these were conducted on grape, lettuce, peach, and strawberry. By averaging the ratios of total 3,5-DCA-containing residues to parent compound in all four crops between 21 and 28 days after the final treatment, BASF proposed a factor of 1.5. The metabolism data BASF selected to derive the average factor are in bold type in Table 1.

Table 1. Plant Metabolism Data Summary.

Crop	Label PHI (days)	Study PHI (days)	Conjugates (%TRR)[a]	Vinclozolin per se (%TRR)	3,5-DCA-Containing residues (%TRR)	Factor (ratio of TRR to vinclozolin) [b]
Strawberry Study 1	0	7	--	83	~94	1.1
		14	--	62	~94	1.5
		31	–	31	~94	3
Strawberry Study 2	0	6	12	79	94	1.2
		23	**33**	**46**	**83**	**1.8**
		39	38	25	78	3.1
		10-23[c]	36	7	90	13
Grape Study 1	21	28	10-15	56	90	1.6
Grape Study 2	**21**	**21**	**4**	**85**	**>90[d]**	**1.2**
Peach	14	21	0	79	84[e]	1.3
		28	**14**	**61**	**84[e]**	**1.6**
		35	31	44	84[e]	2.3
		48	54	25	84	4
Lettuce Study 1	28	0.1	≤5	53	~85	1.6
		6	≤24	34	~85	2.5
		12	≤26	13	~85	6.5
		21	≤37	3	~85	28
Lettuce Study 2	**28**	**28**	**--**	**71**	**88**	**1.2**

[a]TRR = Total Radioactive Residue.
[b]Factors were calculated by HED from ppm equivalents of the TRRs (not presented); factors in bold were apparently included in BASF's average.
[c]Extracts of samples taken at PHIs of 10, 17, 20, and 23 were combined and analyzed.
[d]Estimated by HED.
[e]Assumed by HED to be the same as the value experimentally determined at day 48.

AGENCY RESPONSE

HED would first like to detail the reasons field trial data were initially selected as the most appropriate data set to serve as the source of ARs as opposed to FDA or USDA/PDP monitoring data. Available field trial data, monitoring data, and plant metabolism data were examined to make this selection. Reasons were as follows:

(1) PDP analyzes only vinclozolin per se whereas plant metabolism studies demonstrate that, in many cases, vinclozolin per se is a minor component of the residue.

(2) FDA often analyzes the parent compound as well as Metabolites B and E. However, Metabolites D, F, S, and T are not sought by FDA; these may be present in varying amounts (up to 10% of the TRR) depending on the crop and time posttreatment. More importantly, however, is that conjugates increase dramatically with time as they tend to be more stable and terminal products of detoxification and/or elimination mechanisms. Conjugates often comprise >30% of the TRR within 3 weeks posttreatment, eg. peach and strawberry in Table 1. Other metabolites may also exist.

(3) Field trial data reflect **all** residues of toxicological and regulatory concern, i.e., residues of the parent compound and all residues containing the 3,5-DCA moiety, including conjugates, because the data collection analytical method used includes a base hydrolysis step prior to any residue extraction step that converts all residues of concern to a common moiety.

(4) HED considered the plant metabolism data to be too variable and to leave too much radioactivity unidentified to derive a residue correction factor in which we have sufficient confidence to conduct a human health risk assessment. This is especially true for a late-season, endocrine-disrupting developmental toxicant such as vinclozolin, particularly when at least Metabolites B and E are more potent antiandrogens than the parent compound. Note that, in several cases, plant metabolism study weaknesses were overlooked because the data collection method, with its base hydrolysis step, could be used to demonstrate that, even though unidentified, major portions of the TRR contained the 3,5-DCA moiety.

(5) The time between the last treatment and analysis of monitoring samples is unknown but, if a given sample came from a treated field, this interval would certainly be longer than the minimum preharvest interval (PHI) specified on the pesticide label. As a result, the concentration of the parent compound is likely to be quite a bit lower at consumption than at the label PHI whereas metabolites, particularly conjugates, will have increased proportionately. Correcting ARs derived from monitoring data by a fixed residue factor (as opposed to the true ratio of DCA-containing residues to vinclozolin per se which increases with time) introduces additional error because it reflects the ratio at only one point in time and it tends to underestimate exposure.

HED has included in Table 1 the four additional plant metabolism studies BASF did not use to support their proposed residue correction factor. In response to the BASF

proposal, HED has provided below some of the specific reasons that a factor in which we have sufficient confidence to conduct a human health risk assessment cannot be based on the available metabolism data. These are numbered sequentially with the five more general bases given above.

(6) Results of % parent vs. percent convertible to 3,5-DCA is variable and inconsistent. Only data showing no inconsistencies were presented in the registrant's argument and summary. For example, strawberry study 1 shows a ratios (% convertible to 3,5-DCA/% parent) ranging from 1.1-3 for PHIs ranging from 7-31 days, while strawberry study 2 shows a ratio of 13 for samples taken from the 10- to 23-day time period. Lettuce study 1 gives a ratio of 28 at day 21, while lettuce study 2 gives a ratio of 1.2 at the labeled PHI of 28 days. These inconsistent results make it difficult to estimate an appropriate conversion factor to apply to the PDP data.

(7) The data are not likely to represent the ratios which would be present in PDP samples. There is a clear trend of decreasing amounts of parent over time, with increasing amounts of metabolites of concern. For example, lettuce study 1 shows only 3% parent remaining after 21 days, while the labeled PHI for lettuce is currently 28 days. While a poor translation, lettuce would be the most appropriate data for translation to green beans, a major risk driver for chronic and cancer assessments. Considering the labeled PHI, the potential typical PHIs, and the time the green beans could spend in transit to the point where PDP would sample, the ratio could range from a low of ~5 up to ~30 (e.g., if actual PHI were 15 days and 7 days elapsed before green beans made it to the market).

(8) Consideration of other risk drivers and/or crops BASF is particularly interested in supporting:

Grapes: The use is on wine grapes used for imported wine. Domestic or imported table grape data would not be applicable since use patterns for table vs. wine grapes could be different. If use data were submitted demonstrating that foreign table and wine grapes were treated similarly with vinclozolin, or that table grapes were likely to have higher residues than wine grapes, the metabolism data could be used to generate a factor of about 1.6 for wine grapes. However, the factor applicable to the consumed product, wine, is unknown. This is further complicated by the fact that some data suggest that vinclozolin is extensively metabolized to 3,5-DCA during fermentation. A fermentation study is likely to permit refinement of wine exposure.

Canola: No PDP data exist for canola. If monitoring data were available for parent, the long PHI for this crop (due to the bloom application) would make the data useless - the residue is likely to be virtually all metabolites.

Green beans (fresh only): Discussed above. Data would have to be translated from lettuce which shows variable and inconsistent results from 2 studies.

Green beans (processed/canned): Because of the decrease in parent residues over time, a factor for canned green bean data cannot be determined. It would likely be much higher than a factor determined for fresh green beans.

Strawberries: No longer on labels. However, because of short storage time and relatively consistent metabolism data, a factor could be used.

Stone fruits: No longer on labels. A factor could be determined although it would be relatively high because of the decreased residues over time and the longer storage time for peaches.

Lettuce: Variable and inconsistent results from 2 available studies.

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